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Deterioration of Renal Function Associated with Current Level of Immunodeficiency

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BACKGROUND

Deterioration of renal function (DRF) among HIV-patients is recognized to be caused by traditional renal risk factors, HIV itself, and exposure to antiretrovirals (ARTs). The contribution of immunodeficiency has not been well characterized .

OBJECTIVES

To prospectively evaluate the rate of and factors associated with DRF by assessing changes in estimated glomerular fitration rate (eGFR).

METHODS

Patients

EuroSIDA is a prospective study of patients with HIV-1 infection in 93 centres across Europe (and Israel and Argentina – please see study group). Data is extracted from patient notes onto standardised follow-up forms at 6-monthly intervals.

Patients from the EuroSIDA study were included with the following inclusion criteria:

- a minimum of 3 serum creatinine measurements measured after 1 January 2004 (date from which serum creatinine has been routinely recorded in the EuroSIDA study)
- body weight measured within 12 months of each creatinine measurement
- recorded date of birth

Patients have a maximum of 37 serum creatinine measurements. On average, follow-up is to Autumn 2006.

Statistical methods

eGFR was calculated using the Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations after standardization for body-surface area using the Mostellar formula.

$$GFR\ (CG) = \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72} \times 0.85 \text{ (if female)}$$

$$GFR\ (MDRD) = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (female)} \times 1.21 \text{ (black)}$$

DRF was defined as two consecutive eGFR<60 ml/min/1.73m² or a confirmed 25% decline in eGFR, and baseline was defined as the date of the first eGFR.

For the first analysis, patients whose first GFR < 60 were excluded from the analyses. Patient follow-up began at baseline and ended at the second of 2 consecutive GFR < 60, or at last GFR measurement for patients who did not progress to the endpoint. For the second analysis, all patients were included and patient follow-up began at baseline and ended at the second of 2 consecutive GFR < 75% of baseline GFR, or at last GFR measurement for patients who did not progress to the endpoint.

Table 1

Patient characteristics at baseline

		All	GFR<60	GFR 60.1-90	GFR>90	P
%		N=5526	N=227	N=2013	N=3286	
Gender	Female	23.9	23.3	22.9	24.5	0.41
Race	Non- Caucasians	13.8	11.4	13.5	14.2	0.44
Risk	Hom	45.3	44.9	49.2	42.9	<0.0001
Group	IDU	18.3	10.1	16.6	19.9	
	Het	29.4	33.9	27.1	30.4	
Region	S/A	29.8	30.8	31.5	28.6	<0.0001
	C	30.5	29.5	31.8	29.8	
	N	26.9	27.8	26.1	27.3	
	E	12.8	11.9	10.5	14.3	
Prior AIDS		31.3	48.9	34.8	28.0	<0.0001
HBV	Neg	83.7	78.4	82.8	84.7	0.0004
Status	Pos	7.6	7.9	7.0	7.9	
	Unknown	8.7	13.7	10.2	7.4	
HCV	Neg	69.0	69.2	71.7	67.3	<0.0001
Status	Pos	22.6	18.1	19.3	25.0	
	Unknown	8.4	12.8	9.0	7.7	
HIV- RNA <500		74.5	81.5	78.2	71.7	<0.0001
cART at/before baseline		88.0	97.8	90.5	85.9	<0.0001
Ever taken nephrotoxic drugs		15.6	23.8	18.4	13.4	<0.0001
Median and IQR						
Age	Years	43 (38-51)	61 (52-69)	48 (42-55)	41 (36-46)	<0.0001
CD4	Cells/mm3	453 (310-640)	405 (278-539)	458 (319-638)	456 (305-650)	0.0019
VL	log10 (cp/ml)	1.7 (1.7-2.8)	1.7 (1.7-2.1)	1.8 (1.7-2.4)	1.7 (1.7-3.0)	<0.0001
Nadir CD4	Cells/mm3	148 (55-250)	98 (38-184)	140 (50-238)	155 (60-260)	<0.0001
Baseline	Calendar year	07/04 (05/04-12/04)	07/04 (05-04)	07/04 (05/04-12/04)	07/04 (05/04-12/04)	0.50
eGFR	ml/min/1.73m2	95 (82-110)	53 (48-57)	80 (73-85)	106 (98-118)	<0.0001

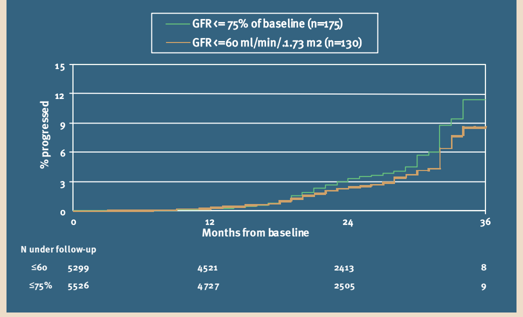
Table 2

Patient characteristics at baseline cardiovascular events

		All	GFR<60	GFR 60.1-90	GFR>90	
%		N=5526	N=227	N=2013	N=3286	P
Acute MI	No	91.0	3.9	90.0	91.9	<0.0001
	Yes	1.4	5.7	2.0	0.8	
	Unknown	7.6	8.4	8.0	7.4	
Carotid	No	92.2	91.2	91.8	92.5	0.64
endarterectomy	Yes	0.1	0.4	0.2	0.1	
	Unknown	7.7	8.4	8.1	7.4	
CABG	No	91.9	89.0	91.4	92.5	<0.0001
	Yes	0.4	2.6	0.6	0.2	
	Unknown	7.7	8.4	8.0	7.4	
Angioplasty	No	91.3	87.7	90.5	92.0	<0.0001
	Yes	1.1	4.0	1.5	0.6	
	Unknown	7.6	8.4	8.0	7.4	
Stroke	No	91.2	86.8	90.8	91.8	<0.0001
	Yes	1.0	4.9	1.0	0.8	
	Unknown	7.8	8,4	8.2	7.4	
Diabetes	No	86.6	76.7	85.4	88.0	<0.0001
	Yes	5.3	15.9	6.2	3.9	
	Unknown	8.1	7.5	8.5	8.0	
Hypertension	No	57.8	46.7	56.0	59.6	<0.0001
	Yes	22.7	37.9	26.4	19.3	
	Unknown	19.5	15.4	17.5	21.1	
Smoking	Never	71.7	70.9	73.8	70.5	0.11
	Current	7.1	9.7	6.7	7.2	
	Past	0.3	0	0.3	0.4	
	Unknown	20.8	19.4	19.3	21.9	

Figure 1

Progression to confirmed low GFR or 75% of baseline (CG)



Multivariable Cox models, stratified by centre, were established. Variables considered for the models were gender, race, age, exposure group, prior AIDS diagnosis, prior use of nephrotoxic drugs (acyclovir, amphotericin B, cidofovir, foscarnet or pentamidine), CD4, viral load and haemoglobin at baseline as well as latest measurement, CD4 nadir, peak viral load, prior atherosclerotic disease (MI, stroke, CABG, or carotid endarterectomy), diabetes (diagnosis of diabetes mellitus prior to baseline, or taking oral antidiabetic agents or insulin at baseline), hypertension (baseline systolic blood pressure ≥ 140 mm/Hg or baseline diastolic blood pressure ≥ 90 mm/Hg or taking antihypertensive agents at baseline) and smoking status. Several ways of modeling use of ART was used including both cumulative and current use of ART.

RESULTS

5526 patients were included. Baseline charcteristics are shown in **table 1** and **table 2**.

During follow-up, eGFR was measured 31650 times (5/patient, IQR 4-7; median time between eGFR 4 months (3-6). Using the CG equation, 130 patients (2.4%) with the mean of the first 2 eGFR >60 ml/min/1.73m² experienced a confirmed eGFR<60 and 175 patients (3.2%) a confirmed 25% decline in eGFR (incidence rates 13.4 (95%CI: 11.1-15.7) and 17.3 (14.4-19.9)/1000 PYFU, respectively); 41 patients experienced both outcomes.

A Kaplan-Meier plot of time to a confirmed eGFR< 60 ml/min/1.73m² or a confirmed 25% decline in eGFR is illustrated in **figure 1**.

In multivariable Cox proportional hazard models, a two fold higher latest CD4 cell count was associated with 31% lower risk of developing a confirmed DRF (adjusted relative hazard (RH)=0.69 (0.55-87), p=0.0034) (**figure 2**). CD4 nadir was not associated with DRF (RH=1.03/two fold higher (0.89-1.19), p=0.74). A prior AIDS diagnosis was associated with increased risk of DRF by 75% (RH=1.75 (1.10-2.79), p=0.018). HCV-antibody positive patients also had an increased risk of DRF (RH=2.67 (1.58-4.52), p=0.0002). Other independent risk factors were diagnosis of a CV event, HIV-RNA levels, baseline eGFR, and time of inclusion into the study.

Repeating the analysis for a confirmed 25% decline in GFR, the adjusted RH per doubling of the CD4 cell count was 0.75 (0.64-0.88), and the results remained essentially unchanged when modelling use of ART in different ways (**figure 3**).

Similar results were obtained using the MDRD equation.

SUMMARY

Deterioration of renal function occurs in 2-3% of the patients over a period of 2-3 years of follow-up.

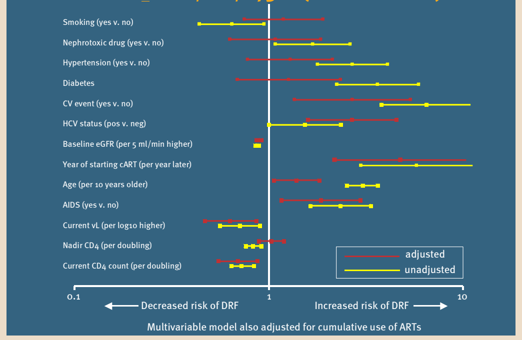
DRF is associated with current levels of immunodeficiency, in addition to traditional risk factors.

A doubling of the CD4 cell count was associated with a 30% reduction in risk of DRF.

Of note, there were wide confidence intervals for many variables in the multivariable analyses, and more exact evaluation of several of these variables require longer follow-up and more endpoints. As follow-up accumulates, the role of ARVs will be further analysed.

Figure 2

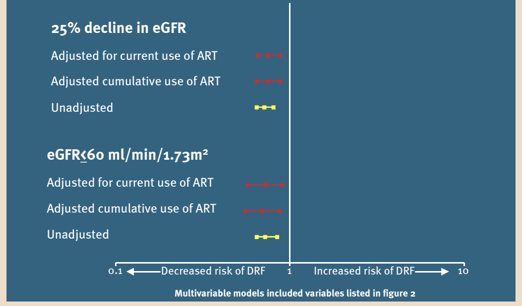
Relative hazards of progression to a confirmed GFR<60 ml/min/1.73m² (Cockcroft-Gault)



Multivariable model also adjusted for cumulative use of ARTs

Figure 3

Role of recent CD4 cell count (relative hazard for doubling of the CD4 cell count) Cox models (Cockcroft-Gault)



Multivariable models included variables listed in figure 2

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